Evidence-Based Procedural Dermatology

Murad Alam
Editor

Second Edition

Springer

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Editor
Murad Alam
Department of Dermatology
Northwestern University
Chicago, IL
USA

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To my parents, Rahat and Rehana Alam,
my sister, Nigar Alam, my nephew Ali,
and my (favorite) niece, Noor.

To my mentors, Ken Arndt, Jeff Dover, David Bickers,
Leonard Goldberg, Randy Roenigk, Ron Moy,
June Robinson, Hal Brody, Scott Dinehart,
Desiree Ratner, Bill Coleman, Tri Nguyen,
Elizabeth McBurney, Amy Paller, Dirk Elston,
Alex Miller, and George Hruza.

Preface to the Second Edition

Since the first edition of this text, much has changed. The methodologic quality of the literature in dermatologic surgery has continued to improve [1, 2]. Journals are encouraging, and authors are accepting, the importance of well-designed studies that are also written up in accordance with appropriate reporting guidelines, like those maintained by Equator [3].

For therapeutic and interventional studies, the importance of carefully selected outcome measures is increasingly apparent. As the Cochrane Collaboration and others have found, research waste can result when the results of small studies cannot be pooled because the outcome measures used are too disparate to reconcile [4, 5]. This problem may ultimately be rectified by the development of core outcome sets, or minimum groups of agreed-upon outcomes that would be employed by all investigators studying a particular disease or condition. In dermatologic surgery, the IMPROVED group is a US-based collaboration working on relevant core outcome sets for the treatment of skin cancers and cosmetic conditions.

High-quality patient-level data may also soon be forthcoming from the many qualified clinical data registries being created by professional specialty societies in the United States. While the presumptive primary incentive for such registries is to facilitate practitioners' ability to report required quality metrics to the federal government, the data collected will also be a fruitful resource for a range of clinical questions. Registries in dermatology, such as DataDerm at the American Academy of Dermatology, are currently "maturing" but within 5 years may be being mined by interested researchers. In dermatologic surgery, the American College of Mohs Surgery has initiated the MohsAIQ Registry, and the American Society for Dermatologic Surgery (ASDS) has planned a registry to track adverse events specifically.

Funds for clinical and comparative effectiveness research in dermatologic surgery are still sparse. A notable bright spot is the ASDS' new Brandt grant program, which specifically supports multicenter clinical research in dermatologic surgery. Investigators are learning to work across centers in ways that are cost- and time-efficient.

The first edition of *Evidence-Based Procedural Dermatology* was named after the ACGME-approved advanced fellowship in dermatologic surgery started in 2003. More recently, this fellowship has been modified to exclude most cosmetic procedures and has been renamed Micrographic Surgery and Cutaneous Oncology (MSDO). A new fellowship program, Cosmetic Dermatologic Surgery, has arisen under the auspices of ASDS to fill the

training gap in advanced cosmetic and laser procedures. Collectively, there are now about 100 fellowship positions in dermatologic surgery each year, with approximately 1 in 4 US dermatology residents choosing to obtain advanced dermatologic surgery training. Perhaps even more importantly, dermatologic surgery is permeating residency training in dermatology, with young dermatologists better trained in the surgical management of relevant conditions. The techniques pioneered by dermatologic surgeons have also entered other specialties, including plastic surgery, head and neck surgery, ophthalmology, vascular surgery, medical and surgical oncology, and many others. As a consequence, this text is more relevant than ever. The growing cadre of specialists in dermatologic surgery need current, authoritative, and comprehensive information that weighs the benefits and limitations of various treatment approaches for conditions of concern.

We have opted to stay with the moniker "Procedural Dermatology," which concisely conveys the breadth of our charge. But the second edition is much expanded from the first. More topics are addressed, and more outstanding chapter authors are included. I am deeply grateful to the many gifted, busy, and generous dermatologic surgeons who have written this book.

Chicago, IL, USA Murad Alam, MD, MSCI, MBA

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Contributors

Sumaira Z. Aasi, MD Stanford University Medical Center, Department of Dermatology, Redwood City, CA, USA

Shino Bay Aguilera, DO SHINO BAY Cosmetic Dermatology, Plastic Surgery & Laser Institute, Ft. Lauderdale, FL, USA

Murad Alam, MD, MSCI, MBA Department of Dermatology, Northwestern Medicine, Feinberg School of Medicine, Chicago, IL, USA

Andrew F. Alexis, MD, MPH Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Department of Dermatology, Mount Sinai St. Luke's and Mount Sinai West, New York, NY, USA

Kenneth Arndt, MD SkinCare Physicians, Chestnut Hill, MA, USA

Sarah T. Arron Department of Dermatology, University of California, San Francisco, San Francisco, CA, USA

Arif Aslam, MD St Helens and Knowsley Teaching Hospitals NHS Trust, St Helens Hospital, St Helens, UK

Marc R. Avram, MD Weill Cornell Medical Center, New York Presbyterian Hospital, New York, NY, USA

Alison Basak, MD, MA Forefront Dermatology, St. Louis, MO, USA

R. Sonia Batra, MD, MSc, MPH Batra Dermatology, Santa Monica, CA, USA

Department of Dermatology, USC Keck School of Medicine, Los Angeles, CA, USA

Christian L. Baum, MD Department of Dermatology, Mayo Clinic, Rochester, MN, USA

Ramona Behshad, MD Department of Dermatology, Saint Louis University, Saint Louis, MO, USA

Daniel A. Belkin, MD Laser and Skin Surgery Center of New York, New York, NY, USA

Daniel Bernstein, MD Icahn School of Medicine at Mount Sinai, New York, NY, USA

Christopher K. Bichakjian, MD Department of Dermatology, Michigan Medicine, Ann Arbor, MI, USA

Kaitlin Blankenship Department of Dermatology, University of Massachusetts Medical School, Worcester, MA, USA

Nina R. Blank, MD Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Diana Bolotin, MD, PhD Section of Dermatology, University of Chicago, Chicago, IL, USA

Jeremy Bordeaux, MD, MPH Case Western Reserve University School of Medicine, Department of Dermatology, Mohs Micrographic and Dermatologic Surgery, Cleveland, OH, USA

David G. Brodland, MD Z & B Skin Cancer Center, Pittsburgh, PA, USA

Departments of Dermatology, Otolaryngology & Plastic Surgery, University of Pittsburgh, Pittsburgh, PA, USA

Brandon Brown, MD University of Florida, Gainesville, FL, USA

Mariah R. Brown, MD University of Colorado School of Medicine, Department of Dermatology, Aurora, CO, USA

Mark E. Burnett, MD, FACMS UPMC Shadyside, Zitelli & Brodland, PC, Pittsburgh, PA, USA

Michael C. Cameron, MD University of Colorado School of Medicine, Department of Dermatology, Aurora, CO, USA

Todd V. Cartee, MD Department of Dermatology, Penn State Hershey Medical Center, Hershey, PA, USA

John A. Carucci, MD, PhD, FACMS Ronald O. Perelman Department of Dermatology, Dermatologic Surgery, NYU Dermatologic Surgical Associates, New York, NY, USA

Paola Chamorro, MD Rutgers-Robert Wood Johnson Medical School, Somerset, NJ, USA

Sean R. Christensen, MD, PhD Department of Dermatology, Section of Dermatologic Surgery, Yale University School of Medicine, New Haven, CT, USA

Armand B. Cognetta Jr, MD Division of Dermatology, Department of Clinical Sciences, Mohs Micrographic Surgery, Florida State University College of Medicine, Tallahassee, FL, USA

Maria Colavincenzo, MD Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Christina Correnti Department of Dermatology, University of Maryland School of Medicine, Baltimore, MD, USA

Martha Laurin Council, MD Division of Dermatology, Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO, USA

Sue Ellen Cox, MD Department of Dermatology, UNC School of Medicine, Chapel Hill, NC, USA

Department of Dermatology, Duke University School of Medicine, Chapel Hill, NC, USA

Ashley Decker, MD Dermatologic Surgery, Cooper University Hospital, Marlton, NJ, USA

Joanna Dong, MD Harbor-UCLA Medical Center, Torrance, CA, USA

Lisa M. Donofrio, MD Yale University School of Medicine, New Haven, CT, USA

Jeffrey S. Dover, MD, FRCPC SkinCare Physicians, Chestnut Hill, MA, USA

Zoe Diana Draelos, MD Department of Dermatology, Dermatology Consulting Services, PLLC, High Point, NC, USA

Daniel E. Edmondson University of Nevada, Reno School of Medicine, Reno, NV, USA

Daniel B. Eisen, MD Clinical Dermatology, University of California Davis Medical Center, Sacramento, CA, USA

Dana L. Ellis, MD Yale School of Medicine, New Haven, CT, USA

Samantha Ellis, MD Department of Dermatology, University of California Davis Medical Center, Sacramento, CA, USA

Sabrina Fabi, MD University of California San Diego, San Diego, CA, USA

Aaron S. Farberg, MD Icahn School of Medicine at Mount Sinai, New York, NY, USA

Hao Feng, MD, MHS New York University School of Medicine, The Ronald O. Perelman Department of Dermatology, New York, NY, USA

Douglas Fife, MD Vivida Dermatology, Surgical Dermatology & Laser Center, Las Vegas, NV, USA

Robert L. Finney, MD, FAAD Cosmetic and Procedural Dermatologist, New York, NY, USA

Bahar Firoz, MD, MPH Rutgers-Robert Wood Johnson Medical School, Somerset, NJ, USA

Stephanie D. Gan, MD Department of Dermatology, University of Michigan, Ann Arbor, MI, USA

Jingyun Gao, MD Section of Dermatology, University of Chicago, Chicago, IL, USA

Roy G. Geronemus, MD Laser and Skin Surgery Center of New York, New York, NY, USA

The Ronald O. Perelman Department of Dermatology, New York University Medical Center, New York, NY, USA

Cerrene N. Giordano, MD Mount Sinai Hospital, New York, NY, USA

Nicholas Golda, MD University of Missouri School of Medicine, Columbia, MO, USA

David J. Goldberg, MD, JD Skin Laser and Surgery Specialists of NY and NJ, New York, NY, USA

Greg J. Goodman, MBBS, FACD, MD, Graddipepi Department of Primary Practice, Monash University, Clayton, VIC, Australia

Skin and Cancer Foundation Inc., Carlton, VIC, Australia

Farzam Gorouhi, MD Department of Dermatology, University of California Davis Medical Center, Sacramento, CA, USA

Shlomit Halachmi, MD, PhD Herzelia Dermatology and Laser Center, Herzelia Pituach, Israel

Jennifer Hau, MD Private Practice, Houston, TX, USA

Amelia K. Hausauer, MD Skin Care and Laser Physicians of Beverly Hills, Los Angeles, CA, USA

H. William Higgins II, MD, MBE Brown University Warren Alpert Medical School, Department of Dermatology, Mohs Micrographic and Dermatologic Surgery, Providence, RI, USA

Shauna Higgins, MD Department of Dermatology, University of Southern California, Los Angeles, CA, USA

Jorge A. Hinojosa, BA Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Sarah Hahn Hsu, MD Maryland Dermatology Laser, Skin & Vein Institute, Hunt Valley, MD, USA

Conway C. Huang, MD Department of Dermatology, University of Alabama at Birmingham, Birmingham, AL, USA

Julie Jefferson, MD, FAAD Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

Nathaniel J. Jellinek, MD Dermatology Professionals, Inc., East Greenwich, RI, USA

Department of Dermatology, The Warren Alpert Medical School of Brown University, Providence, RI, USA

Division of Dermatology, University of Massachusetts Medical School, Worcester, MA, USA

Shang I. Brian Jiang, MD University of California San Diego Health, Department of Dermatology, San Diego, CA, USA

Derek H. Jones, MD Skin Care and Laser Physicians of Beverly Hills, Los Angeles, CA, USA

Division of Dermatology, University of California, Los Angeles, CA, USA

Bridget P. Kaufman, MD Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Arielle N. B. Kauvar, MD New York University School of Medicine, The Ronald O. Perelman Department of Dermatology, New York, NY, USA

New York Laser and Skin Care, New York, NY, USA

Kristen M. Kelly, MD Department of Dermatology and Surgery, University of California, Irvine, CA, USA

Shilpi Khetarpal, MD Department of Dermatology, Cleveland Clinic Foundation, Cleveland, OH, USA

Hooman Khorasani, MD Division of Dermatologic and Cosmetic Surgery, Mount Sinai Health System, New York, NY, USA

Daniel R. Knabel, MD Department of Dermatology, Cleveland Clinic Foundation, Cleveland, OH, USA

Thomas J. Knackstedt, MD Department of Dermatology, Cleveland Clinic Foundation, Cleveland, OH, USA

Nita Kohli, MD, MPH Division of Dermatology, Washington University in St. Louis, St. Louis, MO, USA

Andrew C. Krakowski, MD Division of Pediatric and Adolescent Dermatology, Peds Derm LLC, Bryn Mawr, PA, USA

Rachel Kyllo, MD Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Isabella Lai, MD University of California, Los Angeles, Los Angeles, CA, USA

J. Thomas Landers, MD Department of Dermatology, Naval Medical Center, San Diego, CA, USA

Naomi Lawrence, MD Division of Dermatology, Cooper Medical School of Rowan University, Marlton, NJ, USA

Erica Lee, MD Dermatology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Min-Wei Christine Lee, MD, MPH The Skin and Laser Treatment Institute, Walnut Creek, CA, USA

Department of Dermatologic Surgery, University of California, San Francisco, CA, USA

Henry W. Lim, MD Henry Ford Hospital, Detroit, MI, USA

Ian Maher, MD Department of Dermatology, Saint Louis University School of Medicine, St. Louis, MO, USA

Margaret Mann, MD University Hospitals Cleveland, Case Western Reserve University, Bay Village, OH, USA

Brent C. Martin, MD Department of Dermatology, University of California, Irvine, CA, USA

Melissa McEnery-Stonelake Dermatology and Plastic Surgery Institute, Cleveland Clinic, Cleveland, OH, USA

Ashley McWilliams, MD Department of Dermatology, Saint Louis University Hospital, St Louis, MO, USA

Rachel Miest, MD Dermatology, Rochester, NY, USA

Christopher J. Miller, MD Department of Dermatology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Kira Minkis, MD, PhD New York Presbyterian and Weill Cornell Medical, New York, NY, USA

Kristina Navrazhina, MD, PhD Student New York Presbyterian and Weill Cornell Medical, New York, NY, USA

Kishwer Nehal, MD Department of Dermatology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Isaac Neuhaus, MD Department of Dermatology, University of California San Francisco, UCSF Dermatologic Surgery and Laser Center, San Francisco, CA, USA

Elise Ng, MD Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Iris K. Noh, MD Department of Dermatology, Michigan Medicine, Ann Arbor, MI, USA

Suzan Obagi, MD Department of Dermatology, University of Pittsburgh Medical Center, UPMC Cosmetic Surgery and Skin Health Center, Sewickley, PA, USA

Jeffrey S. Orringer, MD University of Michigan, Ann Arbor, MI, USA

Meredith Orseth, MD University of Texas Southwestern Medical Center, Dallas, TX, USA

Wayne Joseph Overman, MD Oregon Health Science University, Portland, OR, USA

David M. Ozog, MD Department of Dermatology, Henry Ford Hospital, Detroit, MI, USA

Amit G. Pandya, MD Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, USA

David Panther, MD Department of Dermatology, Walla Walla Clinic, Walla Walla, WA, USA

C. Blake Phillips Department of Dermatology, University of Alabama at Birmingham, Birmingham, AL, USA

Kathryn Potter, MD University of Florida, Gainesville, FL, USA

Desiree Ratner Department of Dermatology, NYU Langone Health, New York, NY, USA

Rachel Redenius, MD Department of Dermatology, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Christie Regula, MD Vujevich Dermatology Associates, Pittsburgh, PA, USA

Farhaad R. Riyaz, MD Department of Dermatology, Northwestern University, Chicago, IL, USA

Alyx Rosen, MD University of Miami Miller School of Medicine, Department of Dermatology and Cutaneous Surgery, Miami, FL, USA

Hollywood Dermatology & Cosmetic Specialists, Hollywood, FL, USA

Neil Sadick, MD, FACP, FACPh, FAAD Department of Dermatology, Weill Medical College of Cornell University, New York, NY, USA

Kent Saunders, MD Department of Dermatology, Naval Medical Center, San Diego, CA, USA

Laura M. Schilling, MD Maryland Dermatology Laser, Skin & Vein Institute, Hunt Valley, MD, USA

Renee C. Sheinin, MD Department of Dermatology, Henry Ford Hospital, Detroit, MI, USA

Peter R. Shumaker, MD Department of Dermatology, Naval Medical Center, San Diego, CA, USA

Bryan Sofen, MD UCSF Dermatologic Surgery and Laser Center, San Francisco, CA, USA

Leah K. Spring, DO, FAAD Department of Dermatology, Naval Medical Center Camp Lejeune, Camp Lejeune, NC, USA

Uniformed Services University of the Health Sciences, Bethesda, MD, USA

Divya Srivastava, MD University of Texas Southwestern Medical Center, Dallas, TX, USA

Christopher R. Stamey, MD Department of Dermatology, Yale University School of Medicine, New Haven, CT, USA

Katherine T. Steele, MD Department of Dermatology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

John Strasswimmer, MD, PhD Florida Atlantic University College of Medicine, Boca Raton, FL, USA

Strasswimmer + Smirnov Dermatology, Delray Beach, FL, USA

Drew Taylor, MD Skin Institute of South Florida, Mohs Micrographic Surgery and Dermatologic Oncology Fellowship, Coral Gables, FL, USA

Hollywood Dermatology and Cosmetic Surgery Specialists, Cosmetic Dermatologic Surgery Fellowship, Hollywood, FL, USA

Mohs Micrographic Surgery/Dermatologic Oncology and Cosmetic Dermatologic Surgery, Vail Dermatology, Edwards, CO, USA

Agnieszka K. Thompson, MD Dermatology, Surgery-Dermatologic, Aspirus Dermatology Clinic, Wausau, WI, USA

Andrea Tovar-Garza, MD Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, USA

James V. Twede, MD Department of Dermatology, Mayo Clinic, Rochester, MN, USA

Amanda R. Twigg, MD Department of Dermatology, University of California, San Francisco, San Francisco, CA, USA

Nicole Ufkes Medical University of South Carolina College of Medicine, Charleston, SC, USA

Stefan G. Vanderweil, MD Clinical Instructor, Northwestern Memorial Hospital, Chicago, IL, USA

Gian Vinelli, MD Icahn School of Medicine at Mount Sinai, New York, NY, USA

Abigail Waldman, MD, MHS Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA

Eduardo Weiss, MD, FAAD University of Miami, Department of Dermatology & Cutaneous Surgery, Miami, FL, USA

Florida International University Herbert Wertheim College of Medicine, Dermatology, Miami, FL, USA

Hollywood Dermatology & Cosmetic Specialists, Dermatology, Hollywood, FL, USA

Margaret A. Weiss, MD Department of Dermatology, University of Maryland, Hunt Valley, MD, USA

Robert A. Weiss, MD Department of Dermatology, University of Maryland, Hunt Valley, MD, USA

Reason Wilken, MD Department of Dermatology, University of California Davis Medical Center, Sacramento, CA, USA

Eric C. Wilkerson, MD Skin Laser and Surgery Specialists of NY and NJ, New York, NY, USA

Christopher M. Wolfe Division of Dermatology, Department of Clinical Sciences, Mohs Micrographic Surgery, Florida State University College of Medicine, Tallahassee, FL, USA

Ashley Wysong, MD, MS Department of Dermatology, University of Southern California, Los Angeles, CA, USA

Department of Dermatology, University of Nebraska Medical Center, Omaha, NE, USA

Lindsey Yeh, MD, MS Skin Laser and Surgery Specialists of New York and New Jersey, Hackensack, NJ, USA

Joyce T. Yuan Department of Dermatology, University of California, San Francisco, San Francisco, CA, USA

John A. Zitelli, MD University of Pittsburgh Medical Center, Pittsburgh, PA, USA

David Zloty, MD Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

Designing Randomized Clinical Trials in Dermatologic Surgery

1

Murad Alam

Abstract

There are many ways to better understand how to diagnose and treat our patients. An unusually powerful tool is the randomized controlled trial (RCT). The first well-reported RCT assessed utility of streptomycin for the treatment of tuberculosis in 1948 (Williams, How to critically appraise a randomized controlled trial. In: Williams H, Bigby M, Herxheimer A, Naldi L, Rzany B, Dellavale R, Ran Y, Furue E (eds) Evidence-based dermatology, 3rd edn. Wiley, New York, pp 39–45, 2014). Although a relatively newcomer to the scientific toolbox, the blinded RCT is now widely acknowledged as the key building block that underpins high-level medical evidence.

Keywords

Outcome · Patient · RCT · Surgery · Trial · Intervention · Core

There are many ways to better understand how to diagnose and treat our patients. An unusually powerful tool is the randomized controlled trial (RCT). The first well-reported RCT assessed utility of streptomycin for the treatment of tuberculosis in 1948 [1]. Although a relatively newcomer to the scientific toolbox, the blinded RCT is now widely acknowledged as the key building block that underpins high-level medical evidence.

Potential Benefits of a Blinded RCT [1]

Since performing a blinded RCT is time-consuming and costly, it is helpful to consider why undertaking this burden may be worth the trouble. The specific benefits include reduction of bias and elimination of unknown confounders. Since patients in such a trial are randomly assigned in a concealed manner to two or more groups, patients' characteristics are likely to be similar across groups. Selection bias is therefore avoided. Since outcome assessment is also blinded, we would also expect the absence of detection bias, meaning the outcome of interest is not likely to be observed and measured differently across groups.

The avoidance of unknown confounders is inherent to the randomization process and difficult to achieve in any other experimental design [2]. As an example, let us say we know patients of different ages and genders have different inherent susceptibilities to postoperative dehiscence, and we want to compare two different methods for prevention. We may choose to perform a prospec-

M. Alam (✉)
Department of Dermatology, Northwestern Medicine, Feinberg School of Medicine, Chicago, IL, USA
e-mail: m-alam@northwestern.edu

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tive cohort study, with two groups matched for age and gender. But what if dehiscence rates are also directly correlated with BMI, which we have not considered or matched for? Now, if one preventive technique turns out to be superior, this may be due not to the intrinsic superiority of that technique but to the greater abundance of obese patients in the group receiving the other technique. When we randomize, we need not identify every potential confounder, which is generally impossible. Instead, the process of randomization helps ensure that the prevalence of every confounder is more or less equal in each group.

Elements of a Well-Designed RCT

Power, Sample Size, and Procedure Specification [3, 4]

Before beginning a study, it is crucial to consider, and then to write out in extreme detail, exactly what will be done, step by step. Recruitment, blinding and randomization, interventions, follow-ups, outcomes, and statistical analyses must all be prespecified. It may be helpful to consult with other content experts, as well as epidemiologists and experts in trial design. Study design errors are rectifiable at this stage, but less so later. Failure to prespecify and double-check study design elements before initiating the study may lead to inconsistent or changing study procedures, which impairs the quality of your data.

Also necessary at this time is a statistical analysis. Given the comparison you are trying to make, the primary outcome measure you are planning on using, and the expected difference across groups on this measure, a biostatistician will be able to tell you how many patients you will need to enroll. Depending on the power, or ability to detect a difference, you preselect for your study (typically 0.8 or 0.9 for dermatologic surgery studies), the statistician will be able to tell you the sample size that will likely be sufficient to detect a difference of a particular magnitude, if in fact such a difference exists. Simple power studies can be performed without a statistician's assistance; however, if in doubt as to the accuracy of your calculation, it is preferable to hire a professional who can detect mistakes earlier, thereby saving time and money later. It is possible that the sample size for certain studies may be prohibitive and impractical, and so you may choose not to conduct the study. Conversely, fewer patients than expected may be required, and this may free you and your staff to work on other projects.

Randomization and Blinding

These elements are well described elsewhere, and so we will review them briefly. First, the allocation to groups should be truly random. Alternating enrollment between group 1 and 2 is not random but in fact quite determined. A random number generator or table should be used, as just writing down numbers, say 1 s and 2 s, as they come to you has also been shown to be not random. Finally, the random allocation must be concealed from the investigator assigning patients to groups. Concealment may entail opaque envelopes (although these can sometimes be tampered with or backlit) with randomization information inside that you tear open right when you need to assign [1]. Or you may call another investigator at a different site who may tell you which group is next by clicking on a database link. The specific method should be thought out in advance, with different investigators instructed regarding their roles, so that errors and confusion about the steps required do not inadvertently lead to unblinding. Blinding is important because even a well-meaning unblinded investigator may preferentially assign sicker or needier patients to the intervention believed to be more effective or safer. Alternatively, an investigator with a stake in seeing the success of a particular treatment may allocate to that arm patients who are more likely to respond. Either of these cases would, of course, introduce selection bias. Even when blinding is maintained, by chance alone, randomization can be unsuccessful in creating two or more similar groupings. This is more common with smaller sample sizes, just as it is not uncommon to flip a fair coin and get three heads in a

row, but it is much less likely to have this happen consecutively 300 times. It is customary to include a table showing the salient demographic and other characteristics of the several groups to reassure the reader that randomization was successful.

Importantly, blinding remains important throughout the study, through to the point when results are being analyzed. For many dermatologic surgery studies, especially those assessing skin scar evolution or cosmetic interventions, the primary outcome measure may be visual assessment of outcomes. While live, in-room assessors may capture more information than those who perform delayed assessments based on standardized photographs, photographic assessments are easier to blind. Also, with photographic assessments, it is feasible to compare before and after outcomes, since pictures exist of both. Live assessments are not only notoriously difficult to blind; they are further impractical in that the same observer may not be available to observe each patient at every assessment visit. If there are two blinded rater assessments for each observation, the practical obstacles only grow in magnitude.

Similarity of Interventions and Sham Arms

For intervention trials, which are common in dermatologic surgery, what happens to patients in the two or more groups after assignment should be kept as similar as possible. Patients should be treated identically, except for the intervention(s) being compared across groups. As a counterexample, if those receiving surgery A are receiving care in an air-conditioned, sterile operating room at a flagship hospital and those receiving surgery B are treated in a hot, stuffy procedure room under clean rather than sterile conditions, the perceived better outcomes of surgery A may be attributable to the environment and not the procedure. Another benefit to maintaining similarity across groups is that this may allow the patient to remain blinded as to treatment allocation. This can be particularly helpful in avoiding bias if patient-reported outcomes are among the primary study outcomes. Sometimes, it will be impossible to keep the patient blinded. For instance, if one arm is a laser treatment and one is a cutting surgery, the patient will hear different sounds, feel different types of anesthesia, and ultimately see different types of scars or sequelae at the treatment sites. When possible, sham treatments may be of utility in preserving blinding. For example, if the study is comparing the use or avoidance of cautery during Mohs repairs, those not assigned to the cautery intervention may be kept blinded if the investigator cauterizes pigs' foot tissue at the appointed time, thus creating the sound and smell of cautery, while pressing down on the patient's surgery site. The illusion may be better maintained if all patients in the study have their eyes covered during the procedure. Note that sham treatment arms may not always be ethical, especially if they create substantial additional risk for patients not receiving a particular treatment. Institutional review boards should be asked to carefully vet any proposed sham procedures.

Dropouts and Intention-to-Treat

Studies involving human subjects will commonly have dropouts. After being consented, some patients may fail to come for their initial visit, others may not complete all their interventions, and yet others may miss follow-up visits. To avoid attrition bias, these dropouts should be noted and they should be included in the statistical analysis of the primary outcomes. This is so because while it is possible that dropouts are due to factors unrelated to the study, such as job relocation or unrelated illness, dropouts may also indicate study-related issues, such as adverse events, intraoperative pain, or delayed healing. Intention-to-treat (ITT) analyses take into account everyone who was initially randomized, regardless of whether they completed the study. So-called per protocol analyses just analyze those who completed all of the study procedures. Whenever possible, ITT analyses should be reported in addition to per protocol analyses. Reports of RCTs should also include a flow chart

that graphically illustrates the movement of patients through the study, including dropouts, which are specified by number, reason for exit, and time point of exit.

Appropriate Outcome Measurement

Most RCTs will have primary and secondary outcome measures. Outcome measures should be (1) relevant for the purpose of the study, (2) sufficient but not excessive in number, (3) adequate to capture the patient experience, and (4) inclusive of relevant core outcome measures for the disease or condition studied.

A relevant outcome measure is one that is able to answer the question raised by the RCT. For instance, if a study is comparing infection risk associated with surgery on the ear versus surgery on the lip, a bacterial culture may be a relevant outcome measure. Purulent drainage may also be a relevant feature but overall skin-related quality of life or precise assessment of the resulting scar using a validated scar scale would not be. A fine, well-developed outcome measure can still be entirely inappropriate for a particular study.

While there is a natural tendency to include as many outcome measures as are relevant and feasible, this is not a good practice. At the 5% significance level, there is small risk that a single outcome measure will show a difference across groups by chance alone. However, if five, or a dozen, or more outcomes are evaluated, the chance that at least one will be a false positive is quite substantial. In general, it is best to select a small group of highly relevant outcome measures.

In recent years, there has been increasing interest in understanding the patient experience during medical procedures. We have moved away from a paternalistic model, in which the physician decided what outcomes were most important, to one that asks patients what they prefer and how satisfied they are. It is highly advisable that RCTs now include at least one "patient-reported outcome." Validated scales are available, for instance, FACE-Q for skin cancer [5].

Another concern currently receiving attention is that results of RCTs on similar topics are often difficult to pool due to differences in the outcomes studied [6]. "Core outcome sets" (COS) are minimum groups' outcomes that based on expert and patient consensus should be used in all studies of particular conditions or diseases. Core outcome measures, or specific measures recommended for assessing each of the outcomes in a COS, are also available in some cases. Notably, a core outcome set is a minimum list of outcomes, and it is entirely proper and even expected that individual investigators will choose to assess additional outcomes.

The COMET group [7] maintains a database of currently available core outcome sets, as well as sets in development. The CSG-COUSIN group [8], affiliated with the Cochrane Collaboration, is specifically focused on skin-related COS. The IMPROVED group [9–12], based in the USA, is taking the international lead in developing COS for dermatologic surgery. Investigators in dermatologic surgery planning an RCT should consider consulting these research groups prior to finalizing their outcome measures.

Primacy of Preplanned Analyses

When an RCT is complete, the results are analyzed. As stated before, an ITT analysis should be provided when feasible, even if a per protocol analysis is also performed and reported. It is important that all analyses prespecified in the methods section be executed as planned. Omitting some analyses or changing the way in which others are done is strongly discouraged, as it can be perceived as evidence of cherry-picking or only showing the analyses that prove your point. On the other hand, doing additional analyses after you have completed preplanned analyses *is* allowed. If you choose to perform additional analyses, these should be labeled as ad hoc or unplanned analyses to avoid confusing the reader. Similarly, after you review your planned analyses, you may perceive an unexpected subgroup difference that you then choose to test statistically. Again, you should note that this was an unplanned subgroup analysis. Consider limiting the number of subgroup anal-

yses to those that are most interesting or reasonable. Performing too many comparisons will inevitably increase the risk of false-positive findings.

Complete Reporting of Results

It is important to report all the variables that were planned to be collected and all the analyses planned to be performed. Data tables should be complete, showing everything found, not just the outcomes considered interesting or those that supported the experimental thesis. It is appropriate to focus on the most relevant findings in the discussion section, but the results section should neither be unencumbered by excess editorial commentary nor overly abbreviated or truncated. Complete and clear reporting of all outcomes reassures the reader that there is no selective reporting bias.

Sometimes studies will be negative. In dermatologic surgery, failure to detect a difference may frequently be attributable to a small sample size rather than true absence of difference. RCTs in the field typically enroll a few dozen patients, with this number perhaps sufficient to reveal large differences but not small differences. While negative results may be disheartening for the principal investigator, it is still important to publish or otherwise disseminate the findings. Otherwise, publication bias, or the selective reporting of more positive studies than negative studies, can create a falsely optimistic perception of the effectiveness of an intervention. By reporting small negative studies and employing core outcome sets, investigators can facilitate pooling of their results with other similar studies to provide a more complete picture.

For RCTs, most high-impact journals will require written reports to conform to the CONSORT guidelines [13, 14]. The CONSORT checklist is a brief expression of these rules. Following the checklist ensures that the recommended types of information are included in each of the major subsections of the paper. If the writer wants further instruction on adhering to these reporting rules, there is a long elaboration document that describes each checklist item in detail and offers examples and rationales.

Role of RCTs in Dermatologic Surgery

Dermatologic surgery is responsible for many of the RCTs in dermatology [15, 16]. Every 5 years during the past decade the number of RCTs reported in the journal *Dermatologic Surgery* has doubled. From 2005 to 2010, more than 130 such trials have been published. Also, over a similar period, the reporting of these RCTs improved consistently, with ever greater adherence to the CONSORT reporting criteria [15, 16].

Many of the RCTs in dermatologic surgery are comparative effectiveness studies of surgical and procedural treatments. This is to be expected, because dermatologic surgery is a field that emphasizes therapeutics. Trials have been performed on both surgical interventions to treat skin cancer and other lesions and cosmetic and laser interventions to improve appearance and the visible signs of aging. It is perhaps surprising that so many RCTS have been performed in a procedural field, as the procedural arena has generally been viewed as less hospitable for such investigations. Contributing factors may include the low risk associated with most dermatologic surgeries, as well as the abundance of alternative procedural interventions for many dermatologic indications.

Practical Considerations Regarding RCTs in Dermatologic Surgery

Steps in Study Design, Personnel Management, Subject Recruitment, and Data Collection and Analysis

Randomized control trials are resource intensive. Before embarking on one, it is useful to contemplate how all the necessary elements will be assembled. Once a preliminary clinical question has been suggested for exploration via an RCT, a complete literature search performed by a skilled investigator is typically needed. The output of

this search will more precisely delineate the practice or research gap, with this in turn helping to narrow or redirect the research question. A rough draft of a proposed study plan, including patient selection, methods, analyses, and expected results, is then prepared. Biostatistical consultation and advice from a methodologist or clinical trials design expert may be helpful at this point. Sample size can be assessed and methodological oversights can be corrected before proceeding. Post-intervention follow-ups should be sufficient in number to provide long-term outcomes data but not so many as to unnecessarily deplete clinical resources. Similarly, if a series of interventions are required, as is common in cosmetic studies, these should be sufficient to achieve a measurable result, but not so many that they are prohibitively expensive in terms of equipment, supplies, and staff time. If it is desirable and possible, a sham treatment arm should be considered. Sufficient research personnel should be dedicated to the study, and their roles should be specified: these may include two or more data collectors; at least one investigator responsible for delivering the intervention; several personnel responsible for the randomization sequence and allocation; a senior research associate or staffer to oversee data collection and compliance, possibly an IRB consultant; and one or more biostatisticians, in addition to the principal investigator. A finalized study protocol will then be used to construct an IRB protocol submission. Specialized staff, possibly borrowed from a research core or hired on an hourly or per task basis, may assist with the generation of the IRB protocol, as well as requested revisions. A recruitment plan may be included in the IRB, especially if external advertising and promotion is needed.

After IRB approval is obtained, and before patient enrollment can begin, randomization sequences are prepared and secured. All necessary personnel, including clinical staff, data collection staff, and other research assistants, are apprised of their roles. For complex studies, a detailed standard operating procedure can be developed to ensure that patients receive interventions systematically, with preservation of blinding. A few mock patients may also be enrolled and treated so that the process is well understood by the staff, with any minor discrepancies corrected at this point. If certain process details are uncertain as they were overlooked in the research and IRB protocols, relevant procedures can now be codified to fill these gaps. Before the first patient is enrolled, the study must also be posted on clinicaltrials.gov. For investigators working in research institutions, this may mean working through an intermediary at the institution.

Once data collection commences, at least two primary data collectors are needed to ensure that data loss does not occur due to absence or unavailability. In addition, the investigator(s) or other individual(s) delivering the intervention are usually different and also need to be present. Space and equipment may need to be reserved. Scheduling, even for a study with relatively few subjects, may be a formidable task, as several treatment and follow-up visits may be required for each, and patients may frequently no-show or request rescheduling.

When patients are enrolled, randomized, and treated, their data will need to be carefully recorded. A senior research staffer may routinely review the paperwork submitted by the primary data collectors to confirm data integrity and compliance with IRB reporting requirements. After the first several patients, the research team may reconvene to correct any process problems. Should serious obstacles arise, the study may need to be suspended, modified, and resubmitted to IRB for approval prior to resumption.

Particularly resource-intensive studies may have a preplanned interim analysis, with a stopping rule. Since dermatologic surgery studies are usually extremely safe, a data safety monitoring board is seldom required. Interim analyses may instead be useful for seeing if the expected results have been obtained, which may presage early termination of the study. During the process of the interim analysis, a biostatistician may need to be unblinded but the remaining members of the team should remain blinded, if possible.

Once the study is completed and data collection is over, data tables are prepared for review. If some of the data were on paper and not previously entered into a database, data entry into

appropriate software will precede preparation of data tables. Looking at the data carefully allows the principal investigator to ensure that the data is valid and without error. Planned analyses are then performed by the biostatistician. Based on the outcome of these, additional ad hoc or subgroup analyses may be added. The report of the RCT is then written. This will generally be reviewed by multiple investigators prior to submission for publication.

Resource Allocation and Costs

In summary, performing a high-quality RCT does require resources. Even a small trial requires a significant number of staff with diverse responsibilities, although not all of them need to devote more than a fraction of their time to the endeavor. If the intervention is partly standard of care, and being delivered in standard clinic space, additional clinical staff and space may not be required, but if not, then they may. IRB approval can slow down the process. Recruitment rate can also be a limiting factor. Even with rapid recruitment and an efficient IRB, such as a non-institutional one, the timeline from inception to writeup for a longitudinal RCT in which treatments are delivered and long-term outcomes assessed will seldom be less than 1 year and often closer to 2.

Direct costs of the RCT will include at the very least: IRB submission fees; payment, either hourly or per project, to the biostatistician and methodologist; and the salary fractions of research staff on the study. Equipment or supplies required may also need to be bought, or they may be donated. Another cost may be reduction in efficiency of the clinical enterprise when research procedures are interjected into standard clinic days.

That being said, many dermatologic surgeons have sufficient staff to easily perform RCTs. Post-residency fellows, whether assigned to micrographic surgery and dermatologic oncology or cosmetic dermatologic surgery, may benefit from the research experience and are required to complete at least one research project during their year-long tenure. Clinical nurses and mid-level providers may enjoy participating in research in addition to the regular clinical duties. In Mohs services, histotechs may have downtime at the end of the day when they may be able to help, and these staff are generally very precise and detail-oriented, and as such, possibly well-equipped to review study paperwork. IRB approval is often easy for those in private practice, with high-quality external IRBs requiring as little as a week to approve low-risk studies. Finally, if a biostatistician or methodologist is not available, the dermatologic surgeon may consider reaching out to a colleague more experienced in the conduct of clinical trials for advice or to review a research protocol.

Closing Thoughts

Many, if not most, important questions in the field of dermatologic surgery remain unanswered. Those questions that have been addressed usually have not been definitively settled and await more data and higher-quality investigations. At the other end of the spectrum, dermatologic surgeons work in resource-rich environments where they can easily perform modest-sized RCTs without much direct expense. Indeed, they are already doing so, in large numbers. Moreover, RCTs can productively engage clinical staff, and at least some may find such work interesting. RCTs are particularly exciting for the principal investigator, who in a relatively brief period can develop a question, test it, find an answer, and communicate this to the world. The answer may change practice or it may not. But it will clear up a small mystery, in at least a small way, and thereby be a voyage of discovery for those on board and a valuable addition to our collective scientific know-how.

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2 Outcomes Assessment in Dermatologic Surgery

Murad Alam

Abstract

Whether performing a randomized controlled trial, a cohort study, or a case-control study, it is essential to select the outcomes to be measured (Dupuy et al, Outcome measures. In: Williams H, Bigby M, Herxheimer A, Naldi L, Rzany B, Dellavale R, Ran Y, Furue E (eds) Evidence-based dermatology, 3rd edn. Wiley, New York, pp 71–74, 2014; Alam et al, Rationalizing outcome measures in dermatologic surgery. Curr Derm Rep 4(3):140–146. doi:10.1007/s13671-015-0106-5, 2015; Alam, Evidence based procedural dermatology. In: Maibach HI, Gorouhi F (eds) Evidence based dermatology, 2nd edn. PMPH-USA, Shelton, pp 539–545, 2012). Deciding on appropriate outcomes requires consideration of the purpose of the study, the types of outcomes available, the number of outcomes that may be appropriate, outcomes that are commonly measured, and outcomes that convey patients' perceptions. Closely related to the task of outcomes selection is choosing specific outcome measures to represent these outcomes. For example, if scar appearance is a selected outcome, a particular validated scar scale may be the corresponding outcome measure.

M. Alam (✉)
Department of Dermatology, Northwestern Medicine, Feinberg School of Medicine, Chicago, IL, USA
e-mail: m-alam@northwestern.edu

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Whether performing a randomized controlled trial, a cohort study, or a case-control study, it is essential to select the outcomes to be measured [1–3]. Deciding on appropriate outcomes requires consideration of the purpose of the study, the types of outcomes available, the number of outcomes that may be appropriate, outcomes that are commonly measured, and outcomes that convey patients' perceptions. Closely related to the task of outcomes selection is choosing specific outcome measures to represent these outcomes. For example, if scar appearance is a selected outcome, a particular validated scar scale may be the corresponding outcome measure.

Selecting Outcomes Appropriate for the Clinical Question

Outcomes and outcome measures should be selected so that the underlying clinical question posed by the study can be answered. A study to measure recurrence rates of skin cancer may reasonably use a live clinical assessment by an expert dermatologist or diagnosis based on skin biopsy, but a measure of skin elasticity or color may be less appropriate, even if these features are accurately and precisely assessed.

Types of Outcomes

As there are different types of outcomes, outcome selection requires not just selecting the best individual outcome(s) but also deciding the categories from which to select. Outcomes can be classified by degree of objectivity, from highly objective, like linear distance, to highly subjective, like global assessment of appearance. Intermediate between these may be normed, validated scales for measuring specific parameters, like color or scar. Another way entails dividing outcome measures based on the type of mechanism used to collect the relevant data. In this formulation, outcomes may be measured by devices or machines; text instruments, like normed or validated questionnaires; or unaided humans. Outcomes that are measured by people, like scales and blinded assessments, can be further subdivided into those that are reported by neutral or blinded raters, those by physicians or investigators, and those by patients or participants. Indeed, these outcomes can otherwise be identical, with their valence impacted by who is doing the measuring. Outcomes can also be rated on the degree to which they conform to underlying theories of pathophysiologic mechanism of action. As an example, if an electronic pulse is said to induce apoptosis in basal cell carcinomas, and this apoptosis is said to manifest as increase in skin erythema, then a precise measure of skin erythema may be said to be an appropriate measure of the rate of apoptosis as well as the effectiveness of the electronic pulse. The problem with relying on a story regarding a proposed mechanism of action is that the story, however convincing, may soon be shown to be wrong, or at least incomplete. Yet another classification scheme considers the extent to which an outcome is insensitive to factors other than those it is expected to measure. If the goal is to measure the degree of collagen remodeling induced by an ablative laser 2 months after treatment, a computed photographic measure of cheek volume may be a poor measure since it may be altered not only by collagen thickening but also by residual post-treatment edema, which may be marked even months after such a procedure. Microscopic evaluation of a tissue biopsy may be better for specifically gauging the degree of collagen growth.

Characteristics of a Robust Outcome Measure

Regardless of type, outcome measures should meet three criteria. They should be accurate, precise, and sensitive to change. Accuracy means that they should truthfully measure the underlying construct. So a temperature measuring device should display the actual temperature, as verified by a reference device measuring temperature. Precision refers to how finely the construct being measured can be distinguished. In the case of a temperature gauge, one that measures to within 0.01 ° is less precise than another which measures to within 0.001 °. Sensitivity to change means that the outcome measure should change in response to changes in the relevant stimulus. If the day becomes cooler, the mercury in the thermometer should fall. Measures that are more sensitive to change may be better able to reveal minor differences over the course of a study. If a hair removal laser removes 5% of total hair per unit surface area per procedure, this may be detectable by a 10-gradation hairometer that provides integral values from 0 (no hair) to 10 (maximum hair), but not by a 3-gradation hairometer (1 = no hair, 2 = some hair, and 3 = maximum hair).

Limitations of Objective and Precise Outcome Measures

The choice of outcome measure is not always obvious. While it may seem like an objective, machine-generated statistic that is highly precise and incredibly sensitive to change would be optimal in most cases, this is not always so. An objective measure need not be accurate and despite the sleek, brushed aluminum case in which it is housed may not reflect with fidelity the real underlying construct it purports to represent. To be convincing, any such measure must be validated against a gold standard. One real-life

example that was not thus validated was a device for measuring fine textural change of facial skin introduced a few years ago. With much fanfare, eager acolytes predicted that this would be the optimal way to quantify the minor but definite degree of skin smoothening induced by some topical cosmeceuticals. In fact, it was not clear what the pretty color pictures the device produced were measuring and if these computed images accurately showed smoothness. Furthermore, the high levels of precision and sensitivity to change were punitively extreme. Indeed, washing the face, sweating a little, or just running a hand over the cheek in a sigh would completely change the character of the output.

Instances When Subjective Outcomes Measures Are Preferred

Even when objective measures are not intrinsically flawed, they may not be the most appropriate outcomes to include. In some cases, subjective outcomes and measures may be said to be philosophically superior and better able to measure what is observed. The clearest case is when grading the aesthetic appearance of facial skin. Since patients receive treatment to reduce facial acne scars or diminish the visible signs of aging in order to look better to themselves, family, friends, and colleagues, the best way to measure the success of such procedures is through visual examination by a perceptive human observer. If the patient looks improved to several such observers, then this is sufficient. Even if a highly accurate and precise electron microscope could detect numerous residual flaws, this is not interesting to the patient, whose friends cannot resolve such tiny features.

The Utility of Complex Outcome Measures

Another consideration is the complexity associated with a particular outcome measure. Some validated scales are extremely complex, with many parts and subparts, and may also require time-consuming internal computations. Study participants and data collectors may become exhausted during the measurement process. Unless the quality of these outcome measures is far superior to that of simpler measures, the more complex measures may be more resource intensive than they are worth.

Core Outcome Sets: What They Are and Why They Are Important [4–10]

In recent years, it has become apparent that heterogeneity in outcomes and outcome measures for studies of the same disease or condition lead to research waste. Since the combined results of many similar studies, or meta-analyses, are believed to be more reliable than the results of any single study, it is unfortunate when such studies report different outcomes, and thereby preclude pooling of their data. The leadership of the Cochrane Collaboration has expressed concern that this problem undermines the usefulness of Cochrane systematic reviews, which may defer specific conclusions and instead plead "insufficient evidence." The solution appears to be development of so-called core outcome sets or minimal groups of outcomes that are intended for use in all studies pertaining to a particular disease or condition. Individual investigators can use more than the core set of outcomes, ideally adding the core set to whatever other outcomes they wish to consider.

Core Outcome Sets: How They Are Developed and by Whom

The development of core outcome sets is a laborious process based on literature review and stakeholder consensus. A long list of outcomes is first produced from a literature search and data extraction. Then this is subjected to refinement and lumping by a steering committee. Several rounds of Delphi process are then used to identify the most important outcomes and those with the greatest degree of consensus. Stakeholders involved in the process may include physicians,

other health-care workers, patients, caregivers, support group representatives, researchers, industry representatives, regulators, methodologists, and others. Since the goal is to produce a set of outcomes that are of universal utility, stakeholders are drawn from many countries and diverse environments. The output of the Delphi process is subject to further refinement and lumping. A face-to-face consensus meeting is then convened to approve a small group of outcomes for the core set. Subsequent similar processes, including Delphi consensus, may be used to identify the best outcome measure for each outcome in the core set. The lead international consortium championing core outcome sets and advancing research methodology for developing these is COMET (Core Outcome Measures in Effectiveness Trials), based in the UK and in existence since 2010 [11]. COMET hosts meetings and also maintains a database of core outcome sets in development. CSG-COUSIN [12], based in Germany, is the core outcome set initiative of the Cochrane Skin Group and focuses on outcome measures relevant to dermatology. The IMPROVED (Measurement of Priority Outcome Variables in Dermatologic Surgery) group [13], based in the USA, is taking the lead in development of core outcome sets relevant to dermatologic surgery [5–7].

Patient-Reported Outcomes

Another new trend in outcome selection is the frequent inclusion of at least one patient-reported outcome in clinical trials. Investigators, government regulators and scientists, and private payers have conceded the obsolescence of the paternalistic model in which only physicians decide what should be measured and what is important for patients. It has become clear that patients' estimation of procedure effectiveness, safety, comfort, downtime, cost, overall satisfaction, and other parameters may differ from that of physicians. As those experiencing treatments, patients are obviously uniquely qualified to assess their impact. In fact, sometimes, patients may notice procedure-related effects that physicians have not even thought to measure. Validated, well-designed patient-reported outcome measures now exist for skin cancer treatment as well as facial rejuvenation.

Selecting a Suite of Outcomes

As explained in the preceding paragraph, selection of appropriate outcomes for a clinical study is a complex process. However, selection of outcomes need not be an either/or process. Outcome selection can be inclusive, with several outcomes all measured in a single study. An investigator may start with a condition-specific core outcome set, which may include some objective measures, and perhaps also a validated independent rater questionnaire or photographic assessment, as well as a patient-reported outcome measure. To this, the investigator may add one or more other outcome measures that he or she deems inadequately covered by the core set and specifically relevant to the particular clinical trial at hand.

When to Measure Outcomes

Once outcomes are selected, it must be decided when to measure them. A clinical trial in dermatologic surgery may have several treatment visits followed by several follow-ups. Some outcomes, such as standardized photographs, may be obtained at every visit, and others, like patient-reported satisfaction, may only be elicited a few times, perhaps just at the last visit. Measuring outcomes more often can be helpful in providing a clearer understanding of the impact of an intervention, including the length of post-procedure recovery time, time to maximum benefit, and the duration of persistence of benefit. But many measurements can also fatigue patients and data collectors, resulting in more patient dropouts, excess resource utilization within the research team, and possibly less accurate data. For many aesthetic studies, the most convincing results are long-term outcomes, after edema and erythema have resolved. On the other hand, asking patients to come back more than 6–12 months after treatment is unlikely to be fruitful. Keep in mind that adding two more follow-up visits to a study involving 50

patients means at least another 100 h of data collection, and possibly much more, if patients cancel and need to be rescheduled. Data collection in clinical trials is also often not contiguous, as patients come when they can and when they wish to, so 100 h of data collection may in fact be spread over many weeks, with some wasted time between visits.

Preplanning Outcomes

Outcome selection should occur before enrollment in a clinical trial commences. The methods section of the study protocol and IRB protocol should detail the outcomes that have been chosen, and when they are to be measured, as well as how and by whom. While multiple outcomes and outcome measures might be included, the total number should be judicious. Assessing very many outcomes is not only resource intensive but also increases the risk that at least one of these outcomes shows a difference by chance alone. The 5% significance level is reasonably protective if only one or a few comparisons are performed, but if numerous outcomes are assessed, the likelihood of a false positive arises.

Reporting of Outcomes

The results section of the report of a clinical trial, cohort study, or other clinical studies should present all of the outcomes that were mentioned in the methods section. If these are too numerous or cumbersome to discuss in the text, they may be displayed in tables or figures. Although some outcomes may be relatively more interesting or supportive of the experimental hypothesis, selective results reporting must be avoided, as it can bias the results.

Closing Thoughts

Determining the appropriate outcomes and outcome measures for a study is of primary importance. Haphazard outcome selection can result in research waste, as the data may not be useful or interpretable. There are different types of outcome measures, and a suite of such, including patient-reported outcomes, may be used for a particular study. Inclusion of a core outcome set, if available, can help aggregate the results of a given study with those of other studies of the same disease, condition, or intervention. Outcomes should be measured as often as needed, but not so often as to unnecessarily deplete resources. Reporting of preplanned outcomes should be complete, so that readers can draw their own conclusions.

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Level of Evidence and Strength of Recommendation

3

Murad Alam

Abstract

The purpose of this book is to convey the evidence (Guyatt et al, JAMA 274(22): 1800–1804, 1995; Guyatt et al, JAMA 284(10): 1290–1296, 2000) in support of procedural dermatology therapies for specific indications. After sifting the data, chapter authors provide their assessment in words and numerical ratings. Specifically, findings based on evidence are accompanied by the level of this evidence in parentheses immediately following. At the conclusion of each chapter, a table is provided that lists findings and recommendations, with numbers to represent the associated levels of evidence and strengths of recommendation.

Keywords

Evidence · Strength · Users · Medicine · Level Dermatology

The purpose of this book is to convey the evidence [1, 2] in support of procedural dermatology therapies for specific indications. After sifting the data, chapter authors provide their assessment in words and numerical ratings. Specifically, findings based on evidence are accompanied by the level of this evidence in parentheses immediately following. At the conclusion of each chapter, a table is provided that lists findings and recommendations, with numbers to represent the associated levels of evidence and strengths of recommendation.

Level of Evidence

Level of evidence is a hierarchical measure. At the top are meta-analyses of randomized control trials (RCTs) and individual RCTs, and expert opinion is far lower in the order. The hierarchy is not intended to denigrate the importance of findings supported by lower levels of evidence. Instead, the purpose of the hierarchy is to show the limits of the data. In some situations, RCTs may be impractical and lower levels of evidence may be all that is achievable or at least sufficient to justify therapeutic decisions.

Since the popularization of measures of level of evidence, many specific formulations have emerged [1–3]. Largely similar, these differ mostly in detail and nuance. We have chosen to use the 2009 Oxford scheme [4], shown below. We feel this is intuitive and easy to use, while also being sufficiently granular in its discriminations (Table 3.1).

M. Alam (✉)
Department of Dermatology, Northwestern Medicine, Feinberg School of Medicine, Chicago, IL, USA
e-mail: m-alam@northwestern.edu

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